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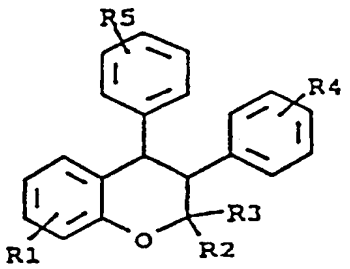
Published
With international search report.

(54) Title: USE OF 3,4-DIPHENYL CHROMANS FOR THE MANUFACTURE OF A PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OR PROPHYLAXIS OF PROSTATIC CARCINOMA

(57) Abstract

The present invention provides novel uses of compounds of formula (I) wherein R^1, R^4 and R^5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, C_{1-6}-alkyl, C_{1-6}-alkoxy or (tertiary amino)(C_{1-6}-alkoxy); and R^2 and R^3 are individually hydrogen or C_{1-6}-alkyl, or as a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of prostatic carcinoma.



(I)

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Use of 3,4-diphenyl chromans for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of prostatic carcinoma.

FIELD OF THIS INVENTION

The present invention relates to the use of compounds of the general formula I for the treatment of patients suffering from prostatic carcinoma and prophylaxis hereof. The present invention also embraces pharmaceutical compositions comprising these compounds and methods of using the compounds and their pharmaceutical compositions.

BACKGROUND OF THIS INVENTION

Cancer of the prostate is the second most common malignancy in men and is the third most common cause of cancer death in men older than age 55. The cause is unknown, but hormonal factors appear to play a role in the development of prostatic cancer. The disease does not occur in eunuchs castrated before puberty, and its incidence is low in patients with hyperestrogenism due to liver cirrhosis. Most cases is diagnosed after the age of 50 years, but they can be seen in younger adults. Total prostatoseminovesicolectomy is the oldest treatment for carcinoma of the prostate. The operation may cause impotence and has its clearest indication only in stage B disease. Radiation therapy has major chronic complications after full courses of treatment and include impotence, chronic proctitis, rectal strictures, rectal fistulas and rectal bleeding. Additionally, current data suggest that radiotherapy may be less curative than radical prostatectomy. Androgen deprivation by means of bilateral orchiectomy, diethylstilbestrol therapy or combined orchiectomy plus diethylstilbestrol has been the standard form of treatment for carcinoma of the prostate for many years. However, recent prospective studies have not demonstrated a clear cut beneficial effect of this type of treatment. Furthermore death from cardiovascular disease appear to be more frequent in patients treated with large doses of diethylstilbestrol. Complete re-

sponse to ordinary chemotherapy (e.g. estramustine phosphate, prednimusitne and cisplatin) is rare and only one-tenth of stage D patients have an objective partial response. Taken together, therefore, the treatment possibilities for this common malignancy is poor.

Centchroman is a non-steroidal compound known to have antiestrogenic activity. It is in use in India as an oral contraceptive (see, for example, Salman et al., U.S. Patent Specification No. 4,447,622; Singh et al., Acta Endocrinal (Copenh) 126 (1992), 444 - 450; Grubb, Curr Opin Obstet Gynecol 3 (1991), 491 - 495; Sankaran et al., Contraception 9 (1974), 279 - 289; Indian Patent Specification No. 129187). Centchroman has also been investigated as an anti-cancer agent for treatment of advanced breast cancer (Misra et al., Int J Cancer 43 (1989), 781 - 783. Recently, centchroman as a racemate has been found as a potent cholesterol lowering pharmaceutical expressed by a significant decrease of the serum concentrations (S.D. Bain et al., J Min Bon Res 9 (1994), S 394).

U.S. patent 5,453,442 describes methods of lowering serum cholesterol and inhibiting smoother muscle cell proliferation in humans and inhibiting uterine fibroid disease and endometriosis in women by administering compounds of formula I as shown therein. Furthermore US patent 5,280,040 describes methods and pharmaceutical compositions for reducing bone loss using 3,4-diarylchromans and their pharmaceutically acceptable salts. There is no disclosure in the patents of using the compounds to treat prostatic carcinoma.

One object of the present invention is to provide compounds which can effectively be used in the treatment or prophylaxis of prostatic carcinoma.

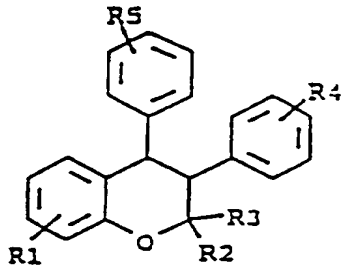
BRIEF DESCRIPTION OF THIS INVENTION

It has, surprisingly, been found that compounds of the general formula I as stated in claim 1 can be used in the treatment or prophylaxis of prostatic carcinoma.

DETAILED DESCRIPTION OF THIS INVENTION

The present invention is based in part on the discovery that a representative 3,4-diarylchroman, centchroman (3,4-trans-2,2-dimethyl-3-phenyl-4-[p-(beta--pyrrolidinoethoxy)phenyl]-7-methoxychroman) effectively decreases prostate weight, inter alia in rats and has been demonstrated to be a partial estrogen receptor agonist. As an increase in prostate weight is generally seen in patients with prostate carcinomas and since estrogen receptor stimulation is the most effective therapy, these data thus indicate that the 3,4-diarylchromans are useful as therapeutic agents against prostatic carcinoma in mammals, including primates such as humans.

Within the present invention, compounds of formula I or their pharmaceutically acceptable salts



(I)

are used for the treatment or prophylaxis of prostatic carcinoma in a patient.

Within formula I, R^1, R^4 and R^5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, C_{1-6}-alkyl, C_{1-6}-alkoxy or (tertiary amino)(C_{1-6}-alkoxy); and R^2 and R^3 are individually hydrogen or a C_{1-6}-alkyl. As used herein, the term "C_{1-6}-alkyl"

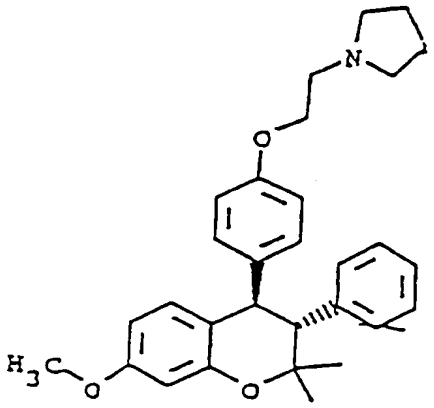
includes straight and branched chain alkyl radicals containing from 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-amyl, sec-amyl, n-hexyl, 2-ethylbutyl, 2,3-dimethylbutyl and the like. The term "C_{1-6}-alkoxy" includes straight and branched chain alkoxy radicals containing from 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, n-amyloxy, sec-amyloxy, n-hexyloxy, 2-ethylbutoxy, 2,3-dimethylbutoxy and the like. "Halogen" includes chloro, fluoro, bromo and iodo. Herein, the term "(tertiary amino)(C_{1-6}-alkoxy)" is a C_{1-6}-alkoxy group which is substituted by a tertiary amino radical. The tertiary amino radical may be a N,N-dialkylamine such as a N,N-dimethylamino, N,N-diethylamino, N,N-dipropylamino and N,N-dibutylamino or a polymethyleneimine, e.g., piperidine, pyrrolidine, N-methylpiperazine or morpholine. Preferred compounds include those in which R^1 is C_{1-6}-alkoxy; R^2 and R^3 are C_{1-6}-alkyl, especially methyl; R^4 is hydrogen; and R^5 is (tertiary amino)(C_{1-6}-alkoxy) of the polymethyleneimine type. Within particularly preferred embodiments, R^1 is in the 7-position and is C_{1-6}-alkoxy, particularly methoxy; each of R^2 and R^3 is methyl, R^4 is hydrogen, and R^5 is in the 4-position and is a (tertiary amino)(C_{1-6}-alkoxy) radical such as 2-(pyrrolidin-1-yl)ethoxy with formula II

(II)

To be included by this invention are all pharmaceutically acceptable salts of the mentioned compounds of formula I.

It is preferred to use the compounds of formula I in the transconfiguration. These compounds may be used as racemic mixtures, or the isolated d- or l- enantiomers may be used. The trans-l-enantiomers are more preferred.

A particularly preferred compound for use within the present invention is centchroman having the formula IV



(IV)

Although only one enantiomer is shown, it will be understood that the formula IV is used herein to designate the transconfiguration of the 3- and 4-phenyl groups and that both the d- and l-enantiomers, as well as the racemic mixture, are included.

3,4-diarylchromans are prepared according to known methods, such as those disclosed in U.S. Patent Specification No. 3,340,276 to Carney et al., U.S. Patent Specification No. 3,822,287 to Bolger, and Ray et al., J Med Chem 19 (1976), 276 - 279, the contents of which are incorporated herein by reference. Conversion of the cis isomer to the trans configuration by means of an organometallic base-catalyzed rearrangement is disclosed in U.S. Patent Specification No. 3,822,287. The optically active d- and l-enantiomers may be prepared as disclosed by Salman et al. in U.S. Patent Specification No. 4,447,622 (incorporated herein by reference) by forming an optically active acid salt which is subjected to alkaline hydrolysis to produce the desired enantiomer. If R^2 is different from R^3 and R^4 is different from R^5, the general formula I covers 8 optical isomers.

Within the present invention, 3,4-diarylchromans of formula I may be prepared in the form of pharmaceutically acceptable salts, especially acid-addition salts, including salts of organic acids and mineral acids. Examples of such salts include salts of organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid and the like. Suitable inorganic acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric and phosphoric acids and the like. The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

3,4-diarylchromans of formula I and their salts are useful within human and veterinary medicine, for example, in the treatment of patients suffering from prostatic carcinoma. For use within the present invention, 3,4-diarylchromans of formula I and their pharmaceutically acceptable salts are formulated with a pharmaceutically acceptable carrier to provide a medicament for parenteral, oral, nasal, rectal, subdermal or intradermal or transdermal administration according to conventional methods. Formulations may further include one or more diluents, fillers, emulsifiers, preservatives, buffers, excipients, etc. and may be provided in such forms as liquids, powders, emulsions, suppositories, liposomes, transdermal patches, controlled release, dermal implants, tablets, etc. One skilled in this art may formulate the compounds of formula I in an appropriate manner, and in accordance with accepted practices, such as those disclosed in Remington's Pharmaceutical Sciences, Gennaro, ed., Mack Publishing Co., Easton, PA, 1990.

Oral administration is preferred. Thus, the active compound of formula I is prepared in a form suitable for oral administration, such as a tablet or capsule. Typically, a pharmaceutically acceptable salt of the compound of formula I is combined with a carrier and moulded into a tablet. Suitable carriers in this regard include starch, sugars, dicalcium phosphate, calcium stearate, magnesium stearate

and the like. Such compositions may further include one or more auxiliary substances, such as wetting agents, emulsifiers, preservatives, stabilizers, colouring additives, etc.

Pharmaceutical compositions containing a compound of formula I may be administered one or more times per day or week. An effective amount of such a pharmaceutical composition is the amount that provides a clinically significant effect against prostatic carcinoma. Such amounts will depend, in part, on the particular condition to be treated, age, weight, and general health of the patient, and other factors evident to those skilled in the art. A typical daily dose will contain a non-toxic dosage range of from about 0.001 to about 75 mg/kg patient per day of a compound of the present invention.

The pharmaceutical compositions containing a compound of formula I may be administered in unit dosage form one or more times per day or week. In the alternative, they may be provided as controlled release formulations suitable for dermal implantation. Implants are formulated to provide release of active compound over the desired period of time, which can be up to several years. Controlled-release formulations are disclosed by, for example, Sanders et al., J Pharm Sci 73 (1964), 1294 - 1297, 1984; U.S. Patent Specification No. 4,489,056; and U.S. Patent Specification No. 4,210,644, which are incorporated herein by reference.

The following examples are offered by way of illustration, not limitation.

Examples of preferred compounds of formula I are centchroman as a racemic mixture and as isolated l-centchroman and d-centchroman enantiomers. Furthermore, 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-hydroxychroman is a preferred compound. The more preferred compound is isolated l-centchroman (l-3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman).

Examples of pharmaceutically acceptable acid addition salts are salts with non-toxic acids, either inorganic acids such as hydrochloric acid, sulphuric acid and phosphoric acid, or organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, succinic acid, gluconic acid, lactic acid, citric acid, ascorbic acid, benzoic acid, embonic acid, methanesulphonic acid and malonic acid.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

Example 1

Sixty sexually mature male Sprague-Dawley rats were assigned to one of the following five treatment groups (12 rats per group): 1)saline, 2) l-centchroman 0.025 mg/kg/day, 3) l-centchroman 0.125 mg/kg/day, 4) l-centchroman 0.625 mg/kg/day and 5) l-centchroman 3.125 mg/kg/day. The doses were administered three times per week for 13 weeks by oral gavage. At the conclusion of the experiment and autopsy was performed, the prostate gland and testes were isolated and weighed.

L-centchroman had no effect on the average testis weight between the groups. However, a marked and dose-dependent effect on the prostate gland was observed as illustrated in Table 1.

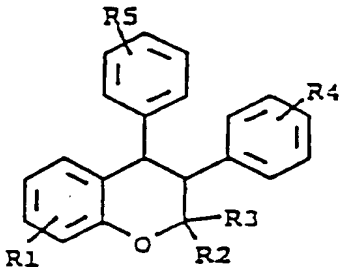
Table 1. Effect of l-centchroman on prostate gland weight in Sprague-Dawley rats

Treatment	Prostate gland (g)
Saline	0.639 ± 0.239
l-centchroman 0.025 mg/kg/day	0.669 ± 0.149
l-centchroman 0.125 mg/kg/day	0.472 ± 0.126*
l-centchroman 0.625 mg/kg/day	0.430 ± 0.122*
l-centchroman 3.125 mg/kg/day	0.368 ± 0.124*

Values are mean ± SD. * indicate significant reduction of prostate gland weight compared to saline treated rats.

CLAIMS

1. The use of compounds of the general formula I



(I)

wherein R^1, R^4 and R^5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, C_{1-6}-alkyl, C_{1-6}-alkoxy or (tertiary amino)(C_{1-6}-alkoxy); and R^2 and R^3 are individually hydrogen or C_{1-6}-alkyl, or as a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of prostatic carcinoma.

2. The use, according to claim 1, wherein R^1 in the compound used is C_{1-6}-alkoxy, R^2 and R^3 are C_{1-6}-alkyl, R^4 is hydrogen and R^5 is (tertiary amino) C_{1-6}-alkoxy.

3. The use according to any one of claims 1 or 2 wherein R^1 is methoxy.

4. The use according to any one of claims 1-3 wherein R^2 is methyl.

5. The use according to any one of claims 1-4 wherein R^3 is methyl.

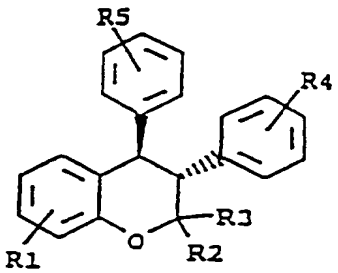
6. The use according to any one of claims 1-5 wherein R^4 is hydrogen.

7. The use according to any one of claims 1-6 wherein R^5 is a group as stated in formula II below:

(II)

8. The use according to any one of claims 1-7 wherein said compound is an isolated d- or l-enantiomer.

9. The use according to any one of the preceding claims wherein said compound has the general formula III as stated below:



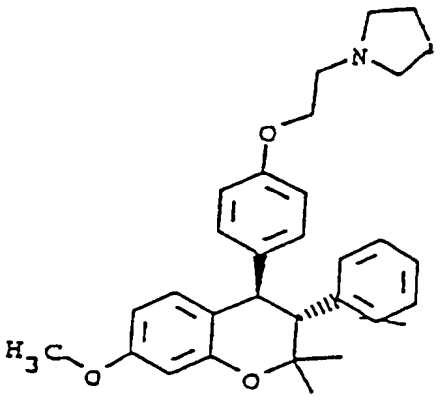
(III)

wherein R^1, R^2, R^3, R^4 and R^5 each are as defined in above claim 1.

10. The use according to anyone of the preceding claims wherein said compound is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-hydroxychroman.

11. The use according to anyone of the preceding claims wherein said compound is an isolated l-enantiomer.

12. The use according to claim 1 wherein said compound is centchroman 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman having the formula IV as stated below:



(IV)

13. The use according to claim 12 wherein said compound is an isolated l-enantiomer of 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman.

14. The use according to any one of the preceding claims wherein said composition is in a form suitable for oral administration.

15. The use according to any one of the preceding claims wherein said compound is administered as a dose in a range from about 0.001 to 75 mg/kg patient per day.

16. The use according to any one of the preceding claims wherein said composition is administered one or more times per day or week.

17. The use according to any one of the preceding claims wherein said composition is in the form of a dermal implant.

18. Method for treatment and prophylaxis of prostatic carcinoma comprising administering to a patient a clinically effective amount of a compound of above formula I stated to be used in any of the preceding use claims, or a pharmaceutically acceptable salt thereof in an amount sufficient to treat or prevent prostatic carcinoma.

19. A method of treating or preventing prostatic carcinoma which method comprises administering a clinically effective amount of compounds and pharmaceutically acceptable compositions, according to previous claims to a patient in need of such a treatment.

20. Any novel feature or combination of features described herein.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00010

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/40, A61K 31/35
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	The Journal of Urology, Volume 137, January 1987, Joseph A. Smith, Jr., "New Methods of Endocrine Management of Prostatic Cancer", page 1 - page 10, see page 4 -- --------	1-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 March 1997	26.04.97
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00010

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 18
because they relate to subject matter not required to be searched by this Authority, namely:
A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [X] Claims Nos.: 20
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 20 is obscure and does not clearly define the matter for which protection is sought, see Article 6.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.